To the editor:

Comparison of rHuEpo plus rHuG-CSF and supportive care: apples to oranges

Casadevall et al recently reported the results of a randomized clinical trial of recombinant human granulocyte colony-stimulating factor (rHuG-CSF) plus recombinant human erythropoietin (rHuEPO) versus supportive care in anemic patients with myelodysplastic syndrome (MDS).1 In our opinion this trial suffers from methodologic flaws that strongly limit its impact on clinical practice.

Studies of rHuEPO cost-effectiveness, particularly as compared with transfusion therapy, are challenging to conduct and analyze. In this regard, the authors should be commended for their good effort. However, the cost of some outcomes, such as quality-of-life (QOL) indicators or the impact of anemia on an individual patient’s productivity, can hardly be quantified. The assessment of the effects of erythropoietic agents and red blood cell transfusion on QOL parameters should also take into account the different targets of the therapies. In fact, current guidelines recommend the use of blood transfusions, which produce a transient benefit, only when patients’ symptoms require immediate action.2 This results in most patients with MDS not being transfused unless their hemoglobin levels are around or below 80 g/L. Conversely, hematopoietic growth factors are generally administered when hemoglobin levels drop below 100 g/L, with the aim of a sustained improvement of anemia. Therefore, a report of the results in terms of quality-adjusted life-years would have probably been more appropriate to assess the relative cost-effectiveness of therapies.3

At this time, the strongest arguments to support the use of erythropoietic agents in cancer patients, including patients with MDS, are the effects on health-related QOL parameters. Most of the studies that have adequately assessed QOL have produced consistent and convincing data indicating an improvement in this end point.4 Patients who have no improvement in hemoglobin levels do not demonstrate an improvement in QOL. The negative results in this trial should be interpreted cautiously because of the small numbers of patients and responders in each group, and it is not clear whether the study was powered to detect differences in the primary QOL measures. Also, since Cronbach alpha was not calculated, there may be doubts regarding the internal consistency of Functional Assessment of Cancer Therapy (FACT-An) scores.

Finally, the design of a trial comparing rHuEpo plus rHuG-CSF with supportive care does not seem entirely appropriate. As the authors correctly remark, there are no randomized trials showing the superiority of rHuEpo plus rHuG-CSF versus rHuEPO alone. On the other hand, there is one randomized, double-blind, placebo-controlled trial involving 87 patients with myelodysplasia showing the efficacy of rHuEpo in relieving anemia relative to supportive care.5 Incidentally, this is the only trial cited in the American Society of Clinical Oncology/American Society of Hematology guidelines to support the use of epoetin in patients with anemia associated with low-risk myelodysplasia.6 On these grounds, a rational approach would have been to carry out a randomized trial between rHuEpo plus rHuG-CSF versus rHuEPO alone. The authors’ statement that synergy exists between rHuEpo and rHuG-CSF is not justified by the results of the present trial.

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Response:

rHuEpo plus rHuG-CSF in the treatment of anemia of myelodysplastic syndromes

We agree with Dr Stasi and colleagues that erythropoietic agents and red blood cell transfusions have different targets: while blood transfusions produce a transient benefit, hematopoietic growth factors aim at obtaining a sustained improvement of anemia. We also agree that randomized controlled trials have some limits: they can answer only some specific questions, in a specific environment and for a limited category of patients. This is particularly the case when cost and quality-of-life evaluation are part of such studies. However, it is now widely recognized that such trials constitute the gold standard of evaluation in medicine, including economic evaluation.7

In our study, we did not compare erythropoietic agents versus blood transfusions but erythropoietic agents supplemented with blood transfusions versus the standard treatment (transfusions alone). Thus, we compared 2 different strategies in terms of effectiveness, cost, and effect on quality of life. We agree with Dr Stasi and colleagues that quality of life is difficult to quantify in
such patients. It is why we decided to use an international, validated quality-of-life instrument, the Functional Assessment of Cancer Therapy (FACT-An) questionnaire.

A quality-adjusted life-year (QALY) takes into account both the quantity and the quality of life generated by health care interventions. It is the arithmetic product of life expectancy and a measure of the quality of the remaining life-years, generating cost-utilities ratios. In QALYs, the amount of time spent in a health state is weighted by the utility score in that health state. A number of approaches have been used to generate quality-of-life evaluation, but only instruments that result in a single score can be used. QALYs, which provide an indication of the benefits gained from a variety of medical procedures in terms of quality of life and survival, can be used in resources allocation decisions. However, QALYs have many limits. In particular, QALYs are not appropriate for diseases where quality of life is a major issue and survival less of an issue, such as myelodysplastic syndromes. In such cases there is a tendency to resort to the use of disease-specific measures of quality of life, as was done in our study. 2

Thus, we do not think that the use of QALYs would have produced better or different results. However, we agree with Dr Stasi and colleagues that our results are limited by the small number of patients, and also by the amount of missing data, as is stated in the discussion part of our article.

Finally, Dr Stasi and colleagues state that, since a randomized trial has shown the efficacy of rHuEpo in relieving anemia in patients with low-risk myelodysplasia, 3 the good design should have been to compare rHuEpo plus rHuG-CSF versus rHuEpo. We apologize for not having cited this article. However, although the results of the trial have been endorsed by the American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) guidelines published in 2002, 4 the level of evidence (level II) and the grade of recommendation (grade B) given in the guidelines are not sufficient to consider rHuEpo the standard therapy of patients with low-risk myelodysplasia. The ASCO/ASH guidelines consider an 8-week trial of epoetin a “reasonable approach” in low-risk myelodysplasia with a low endogenous erythropoietin, but state that the results of the study are limited in terms of generalizability for several reasons (eg, definition of hematologic standards, inadequate information of some baseline data, use of iron supplements). Thus, our study, in which only patients with serum Epo concentrations of less than 500 mIU/mL were included, adds some new information in this debate.

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References

To the editor:

Engraftment of distinct clonal MDS-derived hematopoietic precursors in NOD/SCID-β2-microglobulin-deficient mice after intramedullary transplantation of hematopoietic and stromal cells

Myelodysplastic syndromes (MDSs) are clonal hematopoietic stem cell disorders. In contrast to leukemic cells, however, propagation of MDS-derived clones in vitro or in vivo has proven difficult. 1-3 Thanopoulou et al recently reported the engraftment of human MDS-derived cells in nonobese diabetic–severe combined immunodeficient (NOD/SCID) β2-microglobulin–deficient (β2mnull) mice and NOD/SCID-β2mnull mice transgenically engineered to produce interleukin 3 (IL-3), granulocyte macrophage–colony-stimulating factor (GM-CSF), and SCF. 4 They observed engraftment from 9 of 11 patients with MDS, and in 4 cases, clonal precursors (identified

Table 1. Level of engraftment of human cells in sublethally irradiated NOD/SCID-β2mnull mice

<table>
<thead>
<tr>
<th>Wks after transplantation</th>
<th>Clonal marker (% of cytogenetically abnormal cells*)</th>
<th>Engraftment†</th>
<th>Bone marrow</th>
<th>Spleen</th>
<th>Bone marrow</th>
<th>Spleen</th>
<th>Bone marrow</th>
<th>Spleen</th>
<th>Normal cells/total</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>Blood</td>
<td>Bone marrow</td>
<td>Spleen</td>
<td>Blood</td>
<td>Spleen</td>
<td>Blood</td>
<td>Spleen</td>
<td>Normal cells/total</td>
</tr>
<tr>
<td>4</td>
<td>del(5q)/trisomy8 (95)</td>
<td>58.37</td>
<td>4.44</td>
<td>71.54</td>
<td>NA</td>
<td>24/272</td>
<td>8.8§</td>
<td>5/5</td>
<td>41/44</td>
</tr>
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<td>6</td>
<td>del(5q)/trisomy8; (95‡)</td>
<td>26.06</td>
<td>37.7</td>
<td>27.0</td>
<td>6/61 (9.6)</td>
<td>3/44</td>
<td>6.8§</td>
<td>55/61</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>– Y (75)</td>
<td>0.73</td>
<td>2.11</td>
<td>14.91</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>17</td>
<td>– Y (75)</td>
<td>0.61</td>
<td>1.19</td>
<td>0.09</td>
<td>22/213 (10.3)</td>
<td>0</td>
<td>191/213</td>
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<tr>
<td>6</td>
<td>del(7q) (90)</td>
<td>7.77</td>
<td>0.71</td>
<td>6.1</td>
<td>1/2 (50)</td>
<td>21/218</td>
<td>9.6</td>
<td>1/2</td>
<td>197/218</td>
</tr>
<tr>
<td>13</td>
<td>del(5q) (68)</td>
<td>1.74</td>
<td>0.71</td>
<td>34.19</td>
<td>1/5 (20)</td>
<td>13/201</td>
<td>6.4</td>
<td>4/5</td>
<td>188/201</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td>15.9 ± 9.4</td>
<td>7.8 ± 6.0</td>
<td>25.6 ± 10.5</td>
<td>—</td>
<td>—</td>
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</tr>
</tbody>
</table>

Results determined by flow cytometry (% CD45+ human cells) and FISH analysis for individual mice that underwent transplantation and which are illustrated in the insert. NA indicates not available; —, not applicable.
*Clonal abnormality examined by FISH.
†Percent of CD45+ human cells (illustrated in Figure 1A).
‡FISH results from spleen cells were based on CD45+CD33+ sorted samples; in the other mice FISH results were based on whole bone marrow and spleen cells.
§Only human cells containing an isolated del(5q) were detectable; no cells containing trisomy 8 were identified (illustrated in Figure 1B).
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